Phytodolor® in musculoskeletal disorders: re-analysis and meta-analysis

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Phytodolor® in Musculoskeletal Disorders: Re-Analysis and Meta-Analysis

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Keywords
Herbal medicine · Meta-analysis · Pain · Osteoarthritis · *Fraxinus excelsior* · *Populus tremula* · *Solidago virgaurea* · STW1

Summary
Background: Treatment of rheumatic or musculoskeletal disorders (MD) is multi-disciplinary and includes herbal analgesics. Although already reviewed, no quantitative evaluation of efficacy and safety of the herbal combination Phytodolor® (STW1) is available. **Methods:** We searched in databases and contacted authors and the manufacturer to identify randomized controlled trials (RCTs) examining STW1 in patients with MD. We made a re-analysis of raw data of eligible published and unpublished RCTs and pooled the results for meta-analysis according to Cochrane guidelines and intention-to-treat. Primary outcome measure was patient global assessment of efficacy, secondary outcome measure was pain at rest and on movement. Results were stratified according to treatment groups. **Results:** Patient data of 11 RCTs were eligible for pooling. In the entire population, STW1 was significantly superior compared to placebo in patients' global assessment of efficacy (group difference for rating very good/good: 20%; placebo 48.9% and STW1 69.1%; $p < 0.001$; OR 0.43; 95% CI 0.28–0.65) and in the subpopulation 'other rheumatic diseases' (placebo 45.4%; STW1 72.3%; $p < 0.001$; OR 0.32; 95% CI 0.2–0.52), but not in the subpopulation 'gonarthrosis'. STW1 did not differ significantly compared to non-steroidal anti-inflammatory drugs (NSAIDs), neither in the entire population nor the subpopulations. Similar results were found for pain at rest and on movement. No serious adverse events (AE) but minor AE were reported (placebo 8.1%; STW1 14.2%; NSAIDs 18.9%). **Conclusion:** According to the analysed data, STW1 showed a better pain reduction than placebo in patients with pain due to MD, probably equivalent to NSAIDs, and was well tolerated.

Schlüsselwörter
Phytotherapie · Meta-Analyse · Schmerz · Arthrose · *Fraxinus excelsior* · *Populus tremula* · *Solidago virgaurea* · STW1

Zusammenfassung
Hintergrund: Rheumatische bzw. muskuloskeletale Erkrankungen werden multidisziplinär, einschließlich pflanzlicher Analgetika, behandelt. Obwohl das pflanzliche Kombinationspräparat Phytodolor® (STW1) in Übersichtsarbeiten behandelt wurde, liegt keine quantitative Analyse zur Wirksamkeit und Sicherheit vor. **Methoden:** Wir durchsuchten Datenbanken und kontaktierten Autoren sowie den Hersteller, um randomisierte kontrollierte Studien (RCTs) über STW1 bei Patienten mit muskuloskeletalen Erkrankungen zu finden. Wir führten eine Reanalyse der Rohdaten der geeigneten publizierten und unpublizierten RCTs durch und «poolten» die Ergebnisse für eine Meta-Analyse nach den Cochrane-Richtlinien und «Intention-to-treat». Der primäre Zielparameter war die globale Patientenbewertung der Wirksamkeit, der sekundäre war Schmerz in Ruhe und Bewegung. Die Ergebnisse wurden nach Behandlungsgruppen stratifiziert. **Ergebnisse:** Patientendaten aus 11 RCTs waren zur Poolbildung geeignet. STW1 war dem Placebo bezüglich der globalen Bewertung der Wirksamkeit durch die Patienten sowohl in der Gesamtpopulation (Gruppendifferenz der Anteile mit Bewertung sehr gut/gut 20%; Placebo 48,9% und STW1 69,1%; $p < 0,001$; OR 0,43; 95% CI 0,28–0,65) als auch in der Untergruppe «andere rheumatische Erkrankungen» (Placebo 45,4%; STW1 72,3%; $p < 0,001$; OR 0,32; 95% CI 0,2–0,52) signifikant überlegen, aber nicht in der Untergruppe «Gonarthrose». STW1 unterschied sich nicht signifikant im Vergleich zu nichtsteroidalen Antirheumatika (NSARs), weder in der Gesamtpopulation noch in den Subpopulationen. Ähnliche Ergebnisse fanden sich bei den Parametern Schmerz in Ruhe oder Bewegung. Es traten keine schwerwiegenden unerwünschten Ereignisse auf; nur geringfügige unerwünschte Ereignisse wurden berichtet (8,1% der Patienten mit Placebo; 14,2% STW1; 18,9% NSAR). **Schlussfolgerung:** Entsprechend der analysierten Daten ist STW1 bei Patienten mit rheumatisch bedingten Schmerzen analgetisch wirksamer als Placebo, etwa vergleichbar zu NSAR, und wird gut vertragen.

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Introduction

Musculoskeletal or rheumatic disorders are a major cause of morbidity throughout the world (e.g. osteoarthritis of the knee in 40% of the people over 70) and have a substantial influence on health, quality of life and cost for health systems [1, 2]. Rheumatic diseases are usually associated with pain and loss of function. Due to their mostly degenerative and chronic character, a multimodal long-term therapy with pharmacological and non-pharmacological approaches with several steps in care is required to meet the patients' needs [3, 4]. There is some evidence for the efficacy of herbal drugs, such as topical application of capsaicin [4–7] or oral treatment with extracts from *Harpagophytum procumbens* [8, 9] for pain reduction in osteoarthritis (OA). Yet, not all herbal preparations available today have been analysed in detail. One of those is STW1, known as Phytodolor®, produced by Steigerwald GmbH, Darmstadt, Germany. 100 ml of the standardised herbal combination contain 60 ml of fresh bark and leaves of *Populus tremula* (drug extract ratio (DER) 4.5:1), 20 ml of fresh bark of *Fraxinus excelsior* (DER 4.5:1) and 20 ml of fresh *Solidago virgaurea* (DER 4.8:1); each a 60 vol.-% ethanolic extract. The recommended dose in patients with musculoskeletal disorders (MDs) is usually 20 to 30 drops (40 in severe cases), 3–4 times daily.

In preclinical studies, STW1 has shown several modes of action including the inhibition of cyclooxygenate-1 and -2 (COX-1, COX-2), lipoxygenate (LOX), cytokines, elastase/hyaluronidase [9, 10] and protection of oxidative damage [11]. In rodents, analgesic and anti-inflammatory activities have been shown at doses of 5–10 mg/kg [12].

However, clinical evidence of STW1 seems somewhat inconsistent although reviewed in the literature [6, 9, 13, 14]. Conclusions from systematic reviews range from 'potential (effective) in alleviating pain' [15] or 'suggested reduced pain' [16] or 'moderate support for pain' [7] to 'significant pain reduction' [6]. So far, no meta-analysis has been published to assess the quantitative efficacy of STW1 in patients with MDs, although a meta-analysis was announced in 2007 [13]. A recent review states that a meta-analysis based on the available published trials [9, 14] is all but impossible.

However, STW1 is widely used and one of the leading herbal medicinal combination products in Germany for musculoskeletal complaints, probably because patients prefer herbal medicine as they expect less side-effects compared to non-steroidal anti-inflammatory drugs (NSAIDs) and other analgesics [17, 18].

In this situation, we assumed it to be crucial to evaluate efficacy and safety of STW1 in patients with painful MDs. It was our aim to include published and unpublished studies and to concentrate on patient global assessment as primary outcome, which is suitable in respect of the subjective impairment of patients due to chronic pain. It is widely discussed in general [19–21] as well as in pharmacological [22–24] pain research – even as a primary outcome [24, 25]. In order to perform a rigorous meta-analysis we decided to re-analyse the raw data according to the current standard and to examine whether treatment responses might differ in specific indications (subgroups), e.g. 'gonarthritis'.

Methods

Search Strategy

For this meta-analysis the following databases were retrieved, each from its start till September 2009: AMED, Embase, Cochrane Collaboration, TOXLINE, MEDLINE and HealthSTAR. Search terms were: musculoskeletal disorders, osteoarthritis, pain, Phytodolor®, rheumatic, STW1. Additionally, reference lists from pertinent articles and books were scrutinised, and experts in the field and the manufacturer were contacted.

Selection Criteria

Inclusion criteria for the studies of this meta-analysis were double- or single-blind randomized controlled trials (RCTs) with adequate statistical reporting like intention-to-treat (ITT) analysis or available raw data allowing such an analysis. Studies that did not meet these criteria were excluded. Paucity of the published data led to the inclusion of unpublished studies to compensate publication bias. The primary objective of the review is to assess efficacy and safety of STW1, taking into account clinically relevant endpoints. Due to the great number of unpublished RCTs we decided not to use the Jadad score [26] which was coined to increase internal validity of trial reporting. The guidelines provided by the Cochrane Collaboration Handbook for Reviews [27] have been applied in the analysis of the clinical data.

Study Parameters

In the examined studies, patients with various MDs, e.g. back pain, epicondilitis, spondilitis, rheumatic arthritis or gonarthritis, were treated. The primary endpoint parameter was patient global assessment of efficacy on a 4-point Likert scale (rating: unchanged, moderate, good, very good) because it was uniformly used across the trials in contrast to functional indices like the Schober or Lequesne Index, which had been used only in a few trials. The available secondary endpoints were pain at rest and pain on movement (rating of severity: severe, moderate, mild, absent) and proportion of patients free of the symptom. In 1 RCT [28], pain was measured by visual analogue scale (VAS), whereas the values have been transformed (VAS: 0 = absent; below median at admission = mild; above median at admission = moderate/severe) and have shown comparable validity in this approach [29]. Ratings were available at baseline, day 7, 14 and last visit (mean: 21 days; range: 7–28 days).

Statistics

All included studies were analysed following current standards, pooled and reported as ITT and last observation carried forward (LOCF). To ensure that the meta-analysis of the published and unpublished data was based on a reliable and comparable ground, all raw data from the included RCTs were re-analysed. As a consequence, the findings are not necessarily identical to those given in prior publications.

For stratification trials were allocated into two groups: 'placebo-' or 'NSAID-controlled' (i.e. pooling diclofenac with other NSAIDs). Since a large proportion of the trials dealt with gonarthrosis, we also allocated trials into two subgroups: 'predominantly gonarthrosis' (including 'pure' gonarthrosis in [28]) and 'predominantly other rheumatic disorders' (including some patients with gonarthrosis in [28]).

The studies were tabulated and appropriate software [30] was used for the validation of results. The data were summarised in tables and statistically analysed: In case of dichotomous data, odds ratio (OR) and rate dif-

Table 1. Summary of trials selected (n = 12) and used[a] (n = 11) for meta-analysis

First author, year, design	Design	Duration	Indication	Reference drug	Number of patients			Patient global assessment	Pain on movement	Pain at rest	Allocated to OA knee	Allocated to other rheumatic
					STW1	placebo	reference drug					
Bach, 1994 [28][a]	db	2-day washout, 3 weeks	knee OA	placebo, populus	71 (32/39)	72 (34/38)	72	yes	VAS	VAS	stratified in subpopulations	
Baumann, 1989 [42][a]	db	2 weeks	mainly knee OA	diclofenac	52	0	56	yes	ordinal	ordinal	yes	
Bernhardt, 1991 [36][a]	db/sb	4 weeks	various MD	placebo, sb vs. piroxicam	36	36	36	yes	ordinal	ordinal		yes
Eberl, 1988 [37]	db	1 year	rheumatic arthritis	placebo	20	17	0	yes				yes
Hahn, 1988 [33][a]	db/sb	4 weeks	various MD	placebo; sb vs. indometacin	15	15	15	yes	ordinal	ordinal		yes
Hawel, 1992 [38][a]	db[b]	3-day washout, 3 weeks	various MD	diclofenac	108	0	106	yes	ordinal	ordinal	stratified in subpopulations	
Herzog, 1991 [39][a]	db[b]	7-day washout, 4 weeks	various MD	diclofenac	277	0	140	yes	ordinal	ordinal	yes	
Huber, 1991 [32][a]	db[c]	1-day washout, 3 weeks	various MD, mainly spondilitis	placebo	18	20	0	yes		ordinal		yes
Schadler, 1988 [34][a]	db[c]	2 × 7 days	mainly knee OA	placebo	15	15	0	yes	ordinal		yes	
Schadler, 1988 [40][a]	db	3 weeks	knee OA	diclofenac	15	0	15	yes			yes	
Schreckenberger, 1986 [35][a]	db/sb	1 week	epicondilitis	placebo; sb vs. diclofenac	16	15	15	yes	ordinal	ordinal		yes
Speck, 1990 [41][a]	db	4 weeks	various MD	placebo	37	10	0	yes	ordinal	ordinal		yes

db = Double-blind; sb = single-blind; OA = osteoarthritis; MD = musculosceletal disorders.
[a]Pooled in meta-analysis.
[b]Double-dummy.
[c]Rescue medication.

ference according to Peto Mantel-Haenszel [30] were used; ordinal data were analysed with the $^{2}_{Trend}$ [31] or an equivalent method. In case of continuous data, pooling as weighted mean difference and inverse variance were used. Where appropriate, the number needed to treat (NNT) was given. Sensitivity analyses were performed in the event of significant results. Significance was calculated using two-sided tests, the threshold of significance being $p \leq 0.05$.

For safety analysis only, all studies reporting any safety data (incidence of adverse events (AE)) were included. Most studies reported spontaneous AE.

Results

The research strategy revealed only 1 trial with STW1 in the electronic databases [32]. 13 publications and 28 additional clinical study reports were identified through other channels (42 published and unpublished trials with 3,095 patients: 9 placebo-controlled trials with 205 patients; 12 NSAID-controlled trials with 469 patients and 2 trials of untreated patients with 20 patients). Yet, 30 studies had to be excluded because they were non-comparative or incomplete (e.g. no raw data available, no study report). 12 trials (4 published [32–35], 8 unpublished [28, 36–42]) were retained fulfilling the inclusion criteria (STW1: 680 patients; placebo: 200 patients; NSAIDs: 383 patients; table 1). One had to be excluded because of significant differences between groups at baseline (Ritchie index [37]). 11 RCTs were included in the meta-analysis for efficacy and their raw data could be re-analysed. Female patients slightly outnumbered males by a proportion of 5 to 4 in all treatment groups; age was comparable in the STW1 (57.0 ± 10.2 years) and placebo group (57.3 ± 10.1 years), but in the NSAIDs group patients were older (61.9 ± 10.4 years; $p < 0.001$).

Outcomes

Primary Outcome – Patient Global Assessment of Efficacy in Placebo-Controlled Studies

In the entire patient population, STW1 was significantly superior to placebo (group difference for rating good/very good: 20.3%, placebo 48.9% and STW1 69.1%; $p < 0.001$; OR 0.43; 95% CI 0.28 to 0.65; NNT 4.9; table 2). In the sensitivity analysis, significance was not driven by any particular trial, although it dropped to $p < 0.05$ after elimination of one of the studies [43].

In the subpopulation 'other rheumatic diseases', STW1 was significantly superior to placebo as well (group difference for rating good/very good: 26.9%, placebo 45.4%, STW1 72.3%; $p < 0.001$; OR 0.32; 95% CI 0.2 to 0.52; NNT 3.7; table 2), although it included a small subpopulation of patients with gonarthrosis [28]. In the sensitivity analysis, significance was not driven by any particular trial, too. In the subpopulation with gonarthrosis, no difference was seen in STW1 and placebo.

Table 2. Patient global assessment in placebo-controlled studies

Parameters	All points	Other rheumatic	OA knee
STW1			
Very good	34.0%	35.8%	27.5%
Good	35.1%	36.5%	30.0%
Moderate	22.3%	20.9%	27.5%
Poor	8.5%	6.8%	15.0%
Number	188	148	40
Placebo			
Very good	17.8%	17.0%	20.5%
Good	31.1%	28.4%	41.0%
Moderate	26.7%	27.0%	25.6%
Poor	24.4%	27.7%	12.8%
Number	180	141	39
P-value	<0.001	<0.001	N.S.

N.S. = Not significant; OA = osteoarthritis.

Table 3. Patient global assessment in NSAID-controlled studies

Parameters	All points	Other rheumatic	OA knee
STW1			
Very good	20.0%	30.8%	16.1%
Good	32.8%	36.8%	31.3%
Moderate	27.7%	21.1%	30.2%
Poor	19.4%	11.3%	22.4%
Number	494	133	361
NSAIDs			
Very good	24.5%	24.4%	24.6%
Good	28.4%	33.3%	25.8%
Moderate	27.0%	31.7%	24.6%
Poor	20.1%	10.6%	25.0%
Number	359	123	236
P-value	N.S.	N.S.	N.S.

N.S. = Not significant; OA = osteoarthritis.

Primary Outcome – Patient Global Assessment of Efficacy in NSAID-Controlled Studies

In the entire patient population, STW1 was not significantly different from NSAIDs (group difference for rating good/very good: –0.1%, NSAIDs 52.9%, STW1 52.8%; table 3). In the sensitivity analysis, the outcome was not driven by any particular trial.

In the subpopulation 'other rheumatic diseases', no significant difference was seen (group difference for rating good/very good: 9.9%, NSAIDs 57.7%, STW1 67.7%; OR 0.65; 95% CI 0.39 to 1.09; fig. 1). In the sensitivity analysis, the outcome favoured NSAIDs significantly ($p < 0.05$) after eliminating the corresponding patients from the trial [38].

In the subpopulation 'gonarthrosis', no significant difference was noticed (group difference for rating good/very good: –3.1%, NSAIDs 50.4%, STW1 47.4%; OR 1.13; 95% CI 0.81 to 1.57; fig. 2).

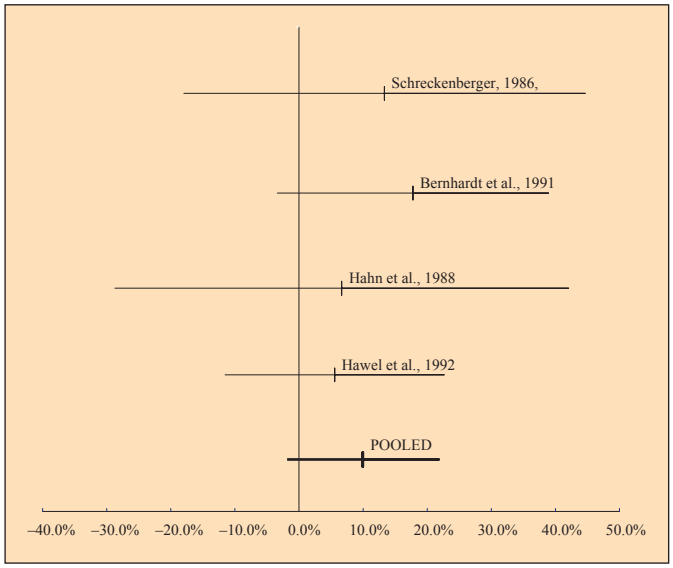

Fig. 1. Plot showing the pooled data of the rate difference between STW1 and NSAIDs in % of patients assessing efficacy 'good/very good' in the subpopulation 'other rheumatic diseases' (mean and 95% CI). Positive differences are in favour of STW1.

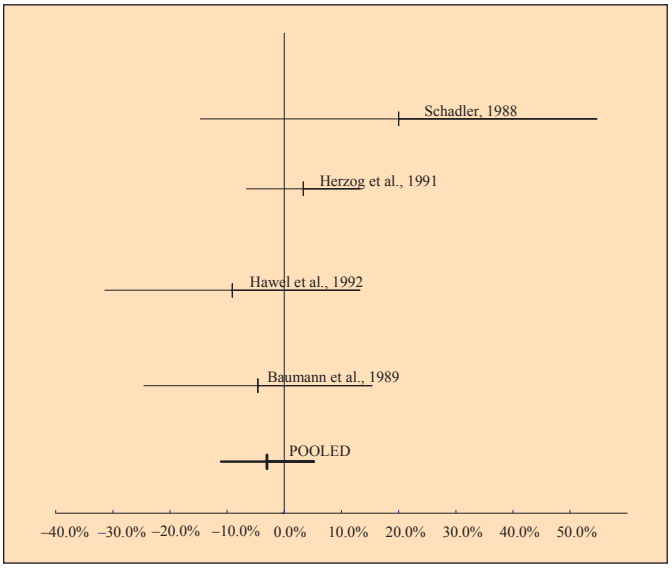

Fig. 2. Plot showing the pooled data of the rate difference between STW1 and NSAIDs in % of patients favouring the rating efficacy 'good/very good' in the subpopulation 'gonarthrosis' (mean and 95% CI). Positive differences are in favour of STW1.

Secondary Outcome – Pain at Rest in Placebo-Controlled Studies

In the entire patient population in the studies that reported on this variable (table 1) for STW1 (n = 141), pain at rest was significantly reduced compared to placebo (n = 143) after 2 weeks of treatment (pain rating: mild/absent; STW1 84.4%; placebo 63.6%; p = 0.003). Yet, this was less evident at last visit (STW1 81.3%; placebo 72.9%; p = 0.046). In the sensitivity analysis, the outcome was not driven by any particular trial, although the difference became significant after exclusion of trials mainly dealing with 'gonarthrosis'. In the subpopulation 'other rheumatic diseases' (n = 252), the difference between treatments was significantly in favour of verum after 14 days (STW1 88.8%; placebo 61.3%) and at last visit (STW1 91.3%; placebo 77.8%; p = 0.014). The high placebo response rate might be explained by the fact that patients additionally had access to rescue medications and other treatments. In the subpopulation 'gonarthrosis', no difference between treatments could be detected at last visit; however, the number of patients was relatively small (n = 40 in each group).

Secondary Outcome – Pain at Rest in NSAID-Controlled Studies

In the entire patient population (table 1), pain reduction was progressive in both treatments, with no significant differences in STW1 (n = 469) and NSAIDs (n = 340). Similar results were observed in the subpopulation 'other rheumatic diseases' (4.8% more pain-free patients with STW1). In the sensitivity analysis, the outcome was not driven by any particular trial and was similar when restricted to diclofenac as reference compound. In the subpopulation 'gonarthrosis', NSAIDs (n = 206) were significantly superior to STW1 (n = 319) at last visit (10% more pain-free patients with NSAIDs; p = 0.006). The outcome in this subpopulation was not driven by any particular trial and was similar when restricted to diclofenac as reference compound.

Secondary Outcome – Pain on Movement in Placebo-Controlled Studies

In the entire patient population (table 1), pain on movement was significantly more reduced with STW1 (n = 136) compared to placebo (n = 136) after 2 weeks (pain rating: mild/absent; STW1 74.3%; placebo 59.6%; p = 0.005) and consolidated at last visit (STW1 79.5%; placebo 62.3%; p < 0.001). The results were similar in the subpopulation 'other rheumatic diseases' (STW1 90.9%; placebo 67.2%), but showed no difference in patients with 'gonarthrosis' (STW1 45.0%; placebo 47.5%). In the sensitivity analysis, the outcome was not driven by any particular trial, neither in the entire population nor in any of the subpopulations. It is interesting to note that more patients became pain-free at rest than on movement, independent of the treatment.

Secondary Outcome – Pain on Movement in NSAID-Controlled Studies

No difference in the reduction of pain on movement in STW1 (n = 495) and NSAIDs (n = 351) could be seen, neither in the entire patient population (table 1) nor the subpopulations at any time during the treatment. In the sensitivity analysis, the outcomes were not driven by any particular trial.

Table 4. AE from patients with reporting; classified according to body system (multiple mentions possible)

Parameters	STW1		NSAIDs		Placebo	
	number	%	number	%	number	%
Patients	660	100.0	381	100.0	198	100.0
Serious AE	0	0	0	0.0	0	0.0
AE	94	14.2	72	18.9	16	8.1
Withdrawal due to AE	29	4.4	12	3.1	3	1.5
Body as a whole	16	2.4	20	5.2	4	2.0
Nervous system disorders	1	0.2	0	0.0	0	0.0
Respiratory, thoracic, mediastinal disorders	0	0	1	0.3	1	0.5
Gastrointestinal disorders	79	12	60	15.7	7	3.5
Hepato-biliary disorders	1	0.2	1	0.3	0	0.0
Skin and subcutaneous tissue disorders	4	0.6	8	2.1	5	2.5
Renal and urinary disorders	1	0.2	0	0.0	0	0.0
Injury and poisoning	1	0.2	0	0.0	0	0.0
Not specified	23	3.5	5	1.3	0	0.0

Safety

In the examined studies no serious AE were reported (table 4). Among the spontaneously reported non-serious AE the hierarchy of incidence was: placebo < STW1 < NSAIDs (significantly more frequent in the STW1 than in the placebo group; $p = 0.03$; less frequent in the STW1 than in the NSAIDs group; $p = 0.048$). The most common AE with both STW1 (12.0%) and NSAIDs (15.7%) were gastrointestinal disorders (e.g. epigastric symptoms), followed by unspecified symptoms such as headache, vertigo and skin disorders (e.g. exanthema). However, AE induced only a few patients to withdraw from the trials (STW1 4.4%; NSAIDs 3.1%; placebo 1.5%). Nevertheless, it is noteworthy that about two-thirds of the non-serious AE with STW1 (14.2%) were reported in one trial [39]. Yet, the authors gave no explanation for this observation. Overall, the frequencies of AE and withdrawals were similar to those observed in a large survey conducted on 1,800 patients (15.6% reported spontaneously AE; 3.2% withdrawals) [44].

Discussion

Patient global assessment of efficacy is used as primary outcome for this meta-analysis, since it was available and also used in pharmacological [22–24] pain research (as primary outcome [24, 25]) and it seems suitable to provide a fair idea of the clinical short-term efficacy of STW1 in patients suffering from limitations due to pain from MDs. While functional indices or biomarkers have been used as outcome measures in MD patients, global assessments seem to be able to measure pain intensity as well as the patients' broader perception of the disease. Therefore, it may provide an accurate and sensitive assessment of the multiple subjective aspects in patients suffering from chronic pain [21]. Global assessments are used in RCTs in OA [24] or rheumatic arthritis [20] as well as in meta-analyses [22]. Furthermore, patient global assessments provided a common global primary outcome parameter in mixed study populations with MDs, such as OA of hip, knee, shoulder, elbow, hands and spinal disorders, while different functional indices would be difficult to compare. Due to stratification of disease groups, the limitations of the treatment with STW1 for OA of the knee became clear as well.

The strength of this meta-analysis is the re-analysis of raw data of each RCT according to current standards and ITT. Nevertheless, there are several limitations such as the single-blind design in studies of STW1 versus reference drugs as well as very short wash-out periods before starting the trials and the short-term intervention in most of the studies. The use of rescue medication and non-pharmacological therapies, which is not unusual in trials with patients suffering from chronic pain, might have contributed to the reduction of any potential difference in treatments.

The main findings of this meta-analysis show that the treatment with STW1 is associated with a good patient global assessment of efficacy, significantly versus placebo; with a significant pain reduction compared to placebo in patients with MDs, but without OA of the knee. The comparison of STW1 and NSAIDs revealed no significant difference of assessments of efficacy in treatments. Pain reduction was rather comparable in MDs, but again not in the OA of the knee. No conclusions can be drawn regarding rheumatoid arthritis. The results of the meta-analysis suggest that there may be different response patterns for articular pain, as seen in gonarthrosis, and other generalized forms of pain, as seen in other MDs, e.g. back pain. This might be an explanation for the delayed onset of the herbal medicinal product, which is no problem in stable chronic conditions, but possibly in inflammatory exacerbatings.

The finding that results of STW1 are better in the placebo-controlled trials, compared to the NSAID-controlled trials, cannot be explained – one might speculate about an unblinding effect.

The tolerance of STW1 in the examined trials shows low rates of spontaneous reporting of AE and is estimated fairly good and somewhat between placebo and NSAIDs.

Conclusions

The presented results for safety and efficacy are encouraging concerning patients global assessment of efficacy and pain reduction in MD but not in OA of the knee. Additionally, this meta-analysis provided information to guide future research with the examined herbal medicinal product: a) RCTs should be sufficiently powered, b) the dosage should eventually be higher and c) long-term treatment needs to be evaluated.

Disclosure Statement

Conflict of interests: None declared.

The Institute of Complementary Medicine (ICM) at the University of Zurich was responsible for the conduct of the project on the following bases: (1) the protocol design and literature searches were the responsibility of the ICM; (2) all data management and analyses were conducted by the ICM, (3) interpretation of results was the prerogative of the ICM and (4) publication of results had to occur regardless of the outcome of the review. Steigerwald AG, Darmstadt, Germany, provided the raw data and partly funded the review.

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